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| 09/774,278      | 01/30/2001  | Gregory M. Lanza     | 4375-000004/US      | 2535             |

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| EXAMINER |
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SHARAREH, SHAHNAM J

| ART UNIT | PAPER NUMBER |
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1617

DATE MAILED: 06/04/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/774,278

Applicant(s)

LANZA ET AL.

Examiner

Shahnam Sharareh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3,7,8,13,14,17-19,25,26,31,32,35 and 68-77 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,7,8,13,14,17-19,25,26,31,32,35 and 68-77 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. Amendment filed on March 24, 2003 has been entered. Applicant's election of the species of ligand, which is at least a portion of an antibody as, set forth in claims 69-71 is also acknowledged. Accordingly, the search is directed to such species. Claims 1,3,7,8,13-14, 17-19, 25-26, 31-32, 35, 68-77 are pending in this application. Any rejection that is not addressed in this Office Action is considered obviated in view of the claim amendments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Claim Rejections - 35 USC § 112***

2. Claims 1,3,7,8,13-14, 17-19, 25-26, 31-32, 35, 68-77 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. All independent claims appear to have omitted the steps of administering the liquid nanoparticles to the target site.

#### ***Claim Rejections - 35 USC § 102***

3. Claims 1; 8, 13, 68-71 stand rejected under 35 U.S.C. 102(b) as being anticipated by Milbrath US Patent 5,401,634.

Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive. Applicant argues that Milbrath's methodologies does not raise the temperature because the energy used in Milbrath's methods are not microwave ranges. (see Amendment at page 7).

First Examiner points out that during patent examination, the pending claims are "given the broadest reasonable interpretation consistent with the specification." MPEP 2111. Second, incorporating limitations of the specification into a claim to thereby narrow the scope of the claim is improper. see also *In re Morris*, 127, F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-1028 (Fed. Cir. 1997). In the instant case, the claims are not only directed to microwave ranges nor are they directed to any degree's of temperature change. Rather, they scope of the claims are directed to such process steps that employs an external energy source directed to a target site bound to fluorochemical containing nanoparticles.

As reasoned in previous Office Action Mailbrath discloses the use of fluorochemical emulsions comprising a fluorochemical droplet having at least one specific binding species immobilized on the fluorochemical droplet which further can contain a surfactant (see abstract, col 6, lines 45-55; col 8, lines 25-40; col 9, lines 18-47; col 14, lines 1-56; col 20, lines 64-69). The droplet size of Mailbrath's emulsion is in the range of 0.01micron (10 nanometer) to 500 microns (see col 7, lines 10-18; col 11, lines 43-57).

Milbrath merely teaches methods of administering nanoparticles containing fluorochemicals to a target site and then applying external energy to perform a spectrophotometric process. Thus, Mailbrath meets all method steps of the instantly claimed invention. Subsequently, the method steps of Mailbrath also inherently is able to raise the temperature of the nanoparticles within the scope of the instant claims. In brief, the instant claims do not exclude the method steps of Mailbrath. Further, applicant

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has not provided any evidence showing the contrary, therefore, the claims stand rejected.

***Claim Rejections - 35 USC § 103***

4. Claims 1,3,7,8,13-14, 17-19, 25-26, 31-32, 35, 68-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger US Patent 5,149,319 (Unger '319) and Trevino et al US Patent 5,733,526 in view of Allen et al US Patent 5,527,528 and Unger et al US Patent 6,123,923 (Unger '921) .

Applicant's arguments with respect to the previous obviousness rejection have been fully considered, however, they are considered moot in view of new grounds of rejection.

Nevertheless, to partially respond<sup>9</sup> to applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Applicant has disregarded the general knowledge in the art that fluorochemicals when exposed to ultrasound energy are conventionally known to cause hyperthermia. Therefore, it is well expected that such compounds are capable of raising the temperature at a local site when exposed to external energy.

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To establish this fact, Examiner draws applicant's attention to Unger '319, because the knowledge generally available to one of ordinary skill clearly would include; for example, such patent. Unger '319 teaches that liquid perfluorocarbons such as perfluorooctyl iodide are hyperthermia potentiators primarily used to convert external energy to local heat (see col 3, lines 55-67; col 8, lines 43-50). Unger further provides that such compounds are administered in the form of emulsions with particle sized of about 5 microns which is about 500 nanometers and well within the size of the instantly claimed nanoparticles. (see col 3, lines 62-67). Further, Unger teaches that such compounds can be encapsulated within a surfactant system (col 4, lines 8-65). In fact, Unger's perfluorocarbons can be used in combination with other therapeutic or diagnostic agents (col 7, lines 62-68). Moreover, Unger's methodology employs an active step of monitoring the progress of the treatment with an ultrasound probe (see examples 5-10). Thus, Unger effectively teaches continuous ultrasound imaging during his methodology.

As Unger 319 was published about 10 years before the instant application was filed, the art to use fluorochemical compounds to raise temperature at a local site by an external energy source was well available to ordinary skilled artisans. Therefore, knowledge generally available in the art would have provided motivation for improving the already known drug delivery systems. Unger's only shortcoming is explicit teaching that his compositions are bound to the target site.

The teachings of Trevino, Allen and Unger '923 have been previously discussed. In short, Trevino teaches compositions can be used as therapeutic and diagnostic

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agents using conventional methodologies (see col 13, line 60-col 14, line 15). The particle size of Treviono's microemulsion are very small in the ranges of less than 100 nm in diameter, thus, Trevino's microemulsion contain nanoparticles (col 18, lines 55-67, col 19, lines 116). Trevino fails to employ a targeting agent or explicitly use an energy source to measure the effects of his composition at a site of interest.

Allen is used solely to show that attaching a targeting agent such as an antibody molecule, to the surface of lipid vesicles is well established in the art employing various methodologies (abstract, col 12, lines 26-col 13, lines 5; also see example 1-3, for different methodologies) and that the targeting agents ensures that the diagnostic or therapeutic vesicles are bound to the site of interest.

Unger teaches emulsion compositions for therapy or imaging comprising nanoparticles, fluorinated gaseous precursors such as perfluorooctane, and targeting ligands (see abstract, col 78, lines 46-60). Unger teaches the use of external energy such as ultrasound or an optical resonating source to scan the site interest (see col 121, lines 19-25; col 123, line 5; col 125, line 15-col 126, line 10). The use of ultrasound energy for imaging or therapeutic purposes are thus well within the level of ordinary skill in the art. Unger fails to explicitly use perfluorooctane liquid in his compositions.

Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the particle sizes of Unger's 319 composition, as taught by Trevino, link a targeting ligand to the particles of Unger '319 by well-known methods, as taught by Allen and Unger '923, and further employ and external source of ultrasound energy as taught by Unger to detect the location of the administered nanoparticles at

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the site of interest. The ordinary skill in the art would have been motivated to do such modifications because as taught by Unger '319 and '923, he would have had a reasonable expectation to improve specificity of the imaging or therapeutic methodologies of choice when employing a liquid fluorocarbon.

### ***Conclusion***

5. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action because the scope of the claims have been modified. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The



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fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123



RUSSELL TRAVERS  
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